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EXAMINER	
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ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/526,829	AGUILAR ET AL.	
	Examiner	Art Unit	
	DiBrino Marianne	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *9/26/05, 10/1/08, 2/26/09, 7/13/09*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-8,11-17,20-42,44 and 46-63* is/are pending in the application.

4a) Of the above claim(s) *14,16,17,20-42,44, 46-48,55,56,58-60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-8,11-13,15,44,49-54,57 and 61-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *7/13/09&3/4/05* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/15/06,1/29/08,5/11/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply with the Sequence Rules*.

DETAILED ACTION

1. Applicant's amendments and responses filed 9/26/05, 10/1/08 and 2/26/09, and Applicant's response filed 7/13/09 are acknowledged and have been entered.

2. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. In particular, SEQ ID NO are required for SEQ ID NO appearing in Table 4 at page 53.

Applicant is advised that for any response to be considered fully responsive said response has to be fully responsive to the sequence compliance requirements.

3. Applicant's election of Group V, and with traverse of the species of class I MHC-binding peptide that has a length of 2-50 amino acid residues and is the tumor peptide SEQ ID NO: 10 (SLLMWITQC) with an Abu substitution at the P9 cysteine, as a peptide that induces agonism and polyclonal CD8+ T cells, and the composition comprising the peptide does not further comprise a non-β-substituted form of the peptide, and composition does not further comprise MHC bound to the peptide, in Applicant's responses filed 10/1/08, 2/26/09 and 7/13/09.

With regard to Applicant's election of Group V, because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP. 818.03(a)).

Applicant's arguments as to traversal of species is of record in the said responses on pages 8-9 and 20-21, respectively.

Applicant's arguments have been fully considered but are not persuasive.

With regard to Applicant's arguments about properties of the elected peptide and these properties not being mutually exclusive, the following applies. A peptide that is 2-15 amino acid residues in length, for example, has the mutually exclusive property of not including peptides that are greater than 15 amino acid residues in length and less than 20, 30 or 40 amino acid residues. A peptide that induces agonism has a different and mutually exclusive structure and function than one that induces tolerance. A peptide that binds class I MHC has a different length than one that binds to class II MHC, the class I MHC peptide does not

bind to class II MHC, and the class I MHC peptide induces CD8+ T cells but not CD4+ T cells as does a class II MHC peptide.

With regard to Applicant's argument alleging no undue search burden in searching the peptide species recited in instant claim 54 because they all contain a common sequence element SLLMWIT, the recited peptides have different sequences and require different sequence searches, even though two are subsequences of the third, and all contain the said common sequence element. A search of the longest peptide, SEQ ID NO: 11 would not necessarily produce hits on the two shorter peptides, SEQ ID NO: 9 and 10. In addition, the common element is not a recited limitation with a SEQ ID NO.

With regard to Applicant's argument about patent term, Applicant is reminded that when the first restriction requirement was mailed, only claims 1-45 were pending. Subsequently, Applicant amended the pending claims and added new claims 46-63.

The requirement is still deemed proper and is therefore made FINAL.

Claims 4-8, 11, 12, 44, 49-54, 57 and 61-63 read on the elected species.

Upon consideration of the prior art, examination has been extended to include the species of virus derived peptide recited in instant claim 13 as well as the species of tolerogenic epitope recited in instant claim 15.

Accordingly, claims 14, 16, 17, 46-48, 55, 56 and 55-60 (non-elected species of Group I) and claims 20-42 (non-elected Groups I-IV and VI) are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Claims 4-8, 11-13, 15, 44, 49-54, 57 and 61-63 are currently being examined.

4. The use of the trademarks MILLI Q, SUPERDEX and MONO Q have been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

5. The disclosure is objected to because of the following informalities: Applicant is required to amend the specification to disclose SEQ ID NO for sequences appearing in the specification, for example, at Table 4.

Appropriate correction is required.

6. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

7. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the Examiner on form PTO-892, they have not been considered.

8. Replacement drawings were received on 7/13/09. These drawings are acceptable.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 11-13, 15, 49-53 and 57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant has broadly claimed a composition comprising a β-amino acid substituted peptide (that is a tumor derived (claim 11) peptide, such as from the tumor antigens recited in instant claim 12, or virus derived (claim 13) and/or may be tolerogenic, *i.e.,* have the function of being tolerogenic (claim 15). Applicant has also broadly claimed a peptide/composition thereof, wherein said peptide comprises a MHC epitope (*i.e.,* it has the functional properties of binding to a MHC molecule and of inducing an immune response *in vivo*) of an antigen with the proviso that the peptide comprises at least one β-amino acid substitution at an MHC anchor position in the said epitope (claims 49 and 57), including a class I MHC epitope (claim 50), including of a tumor derived peptide (claim 51) from the recited tumor antigens (claims 52 and 53).

The peptide in the composition is claimed merely by being peptide “derived from” the universe of all peptides, including from a tumor or viral protein from the universe of all tumor or viral proteins, including the recited tumor proteins, wherein the peptide comprises a β-amino acid substitution of any type at any

position in the peptide and/or having some recited length. The limitation "derived from" may encompass variants of a protein, with only one amino acid residue in common from the protein.

The peptide is claimed by the functional property of being a "tolerogenic epitope" and the structural property of having a β-amino acid substitution of some type at some position in the peptide, without having disclosure of the primary structure of the peptide or the protein from which it is derived (claim 15). There is no disclosed correlation, even if the primary sequence of the peptide were known, between a string of amino acid residues that are comprised in a peptide and the presence of a β-amino acid residue, even if the position of that β-amino acid residue and its identity were known, between that structure and the function of being 'tolerogenic.'

The peptide is claimed by being a MHC epitope of the thousands of MHC allele products that are known to exist, and including wherein the peptide epitope has at least one β-amino acid substitution at an MHC anchor position in the said epitope, and the epitope is from the universe of any protein that exists, including from any tumor protein and including from the recited tumor proteins. There is no known correlation, even if the primary of the peptide were known, between a string of amino acid residues that are comprised in a peptide and the presence of a β-amino acid residue, even if the position of that β-amino acid residue and its identity were known, between that structure and the function of being "an MHC epitope of an antigen", *i.e.,* of binding to an MHC molecule and being immunogenic *in vivo*.

The instant claims are drawn to a product, not to a method for epitope discovery and modification.

The guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, § 1 "Written Description" Requirement make clear that if a claimed genus does not show actual reduction to practice for a representative number of species, then the Requirement may be alternatively met by reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Fri. January 5, 2001, see especially page 1106 column 3).

The MPEP states that for generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP 2163. Although the MPEP does not define what

constitute a sufficient number of representative species, the Courts have indicated what do not constitute a representative number species to adequately describe a broad generic. In Gostdli, the Court determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. In re Gostdli, 872 F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, the claims encompass a claimed product that has substantial variance in that the amino acid sequence is highly variable, the class I molecule for which the sequence is an epitope is highly variable and the portion of a protein that can serve as an epitope is highly variable based upon both MHC binding and other aspects such as in vivo T cell precursor frequency and repertoires, and the β-amino acid substituent identities and positions in the sequence are highly variable. The definition in the specification of β-amino acid residue is an amino acid that differs from an alpha amino acid in that there are two carbon atoms separating the carboxyl terminus and the amino terminus (page 22 at lines 13-15).

The instant specification discloses a positional scan of the SIINFEKKL ovalbumin peptide with each individual successive position substituted with the corresponding β-amino acid, *i.e.,* β-SIINFEKKL, Sβ-IINFEKKL, *etc*, and testing of each peptide for binding to its MHC class I restriction element (H-2Kb), serum stability and CTL antagonism (Examples 1-6).

The specification discloses some exemplary amino acid substitutions, such as for example, β-Ser for Cys, or β-Ile or β-Val for Leu (Table 3 spanning pages 30-31). The specification discloses in a prophetic manner that MHC epitope peptides may be β-amino acid substituted, and that the NY-ESO-1 peptide 157-165 may be substituted at P9 with Abu or Ser (see entire specification, especially paragraph spanning pages 67-68).

This species coupled with some exemplary amino acid substitutions is not representative of all species that fall within the genus because this species has a different primary structure from that of other epitopes, the identity of the b-amino acid residue is different from the universe of potential β-amino acid residues that exist, and each β-substituted peptide is tested to determine if it has the function of binding to the particular MHC molecule the particular correlative native peptide binds to (not to mention no correlation between structure and function of being immunogenic as an epitope or tolerogenic). As enunciated supra in this rejection, the genus is highly variable for the reasons discussed herein.

Therefore, it appears that the instant specification does not adequately disclose the breadth of the claimed peptide/composition thereof recited in the instant claims. In light of this, a skilled artisan would reasonably conclude that Applicant was not in possession of the genus of all claimed β-substituted peptides at the time the instant application was filed.

11. For the purpose of prior art rejections, the filing date of the instant claims is deemed to be the filing date of PCT/AU03/01150*, i.e.,* 9/4/03, as the parent application Australia 2002951212 does not support the claimed limitations of the instant application. The said parent application, *at a minimum*, does not provide support for the genus of β-substituted peptide and composition thereof, except for one sub-genus that is a MHC binding peptide. It does not provide support for the length limitations recited in instant claims 4-8, except wherein the β-substituted peptide comprises *a contiguous sequence* of the recited lengths, nor wherein the peptide is a tumor derived peptide, nor including from the tumor proteins recited in instant claims 12, 52 and 53, nor wherein the peptide comprises at least one β-substitution at a MHC anchor position in the said peptide, nor wherein the MHC epitope peptide is one recited in instant claims 54 and 61-63, nor that the cysteine residue in the sequences recited in claim 61 is β-substituted, including with Abu.

12. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 4-8, 15 and 44 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 01/29081 A1 (IDS reference).

WO 01/29081 A1 teaches a pharmaceutical composition comprising a modified peptide with at least one β-amino acid substitution, said analogue peptide being tolerogenic, and the native peptide is amino acid residues 263-275 of human cartilage gp-39 protein, a class II MHC epitope peptide (especially abstract, page 3 at lines 6-18, Tables 2-3, pages 34-35 and examples 15-16).

14. Claims 4-8, 13 and 44 are rejected under 35 U.S.C. 102(b) as being anticipated by Steer *et al* (Curr. Med. Chem. 4/15/2002, 9(8): 811-822, IDS reference).

Steer *et al* teach compositions comprising β-substituted peptides (see entire reference), such as for example, a pharmaceutical composition (*i.e.,* in PBS) comprising a β-substituted angiotensin II peptide DRVYIHPF, in which Asp-1 was replaced by β-D-Asp or β-L-Asp (especially section 2 on page 812), or a pharmaceutical composition comprising a series of bradykinin analogue peptide RPPGFSPFR containing a β-Pro-7 or β-Phe 8 substitution (especially column 1 on page 813 at paragraph 2), or a pharmaceutical composition comprising a bombesin antagonist peptides based upon D-PQWAVGHLL with a variety of β–substitutions (paragraph spanning columns 1-2 on page 813). Steer *et al* also teach a β-substituted analog of a class I MHC epitope peptide GRAFVTIGK viral peptide that contains β-Ala replacing the FVTIG segment of the peptide that are

TCR contact residues for designing a TCR antagonist peptide (especially paragraph spanning columns 1-2 on page 818).

15. Claims 4-8, 13, 44, 49, 50 and 57 are rejected under 35 U.S.C. 102(b) as being anticipated by Micheletti *et al* (Immunol. 1999, 96: 411-415).

Micheletti *et al* teach a class I MHC epitope peptide and a composition thereof further comprising PBS, a pharmaceutically acceptable carrier, said peptide having the β-amino acid Abu substituted at the position 2 anchor residue for the naturally occurring P2 anchor residue of the HLA-A11 binding peptide. The native peptide corresponds to amino acid residues 416-424 of the EBV nuclear antigen-4 (EBNA4, a viral antigen) (see entire reference, especially Table 1).

16. Claims 4-8, 11, 44, 49-51 and 57 are rejected under 35 U.S.C. 102(b) as being anticipated by Guichard *et al* (J. Med. Chem. 2000, 43: 3803-3808, IDS reference).

Guichard *et al* teach a HLA-A2-binding peptide from tumor antigen Melan-A/MART-1 with a beta amino acid residue substituent at anchor position 2 of the peptide. Guichard *et al* also teach β-amino acid substituents at other positions of the peptide, and compositions comprising each of the peptides. Guichard *et al* further teach that the MART-1 peptide has weak immunogenicity, hence the amino acid substitutions were made in order to study the issue of overcoming said weak immunogenicity. Guichard *et al* that "despite encouraging results, early vaccination trials with peptides derived from gp100, MART-1, tyrosinase, MAGE-1 and MAGE-3 have experienced difficulty in inducing CTL immunity. Guichard *et al* teach that they found that in the case of the MART-1 peptide, each central P3-P7 residue with the exception of P5 could be replaced by the corresponding β-amino acid residue without affecting the ability to bind to HLA-A2 molecules (see entire reference, especially Table 1).

A with regard to the limitation "pharmaceutically acceptable diluent", although the art reference does not teach the diluent that the peptides are comprised in, it does teach that the peptides are in a solubilizing medium, and it also teaches that in the CTL assay, the peptide was added to the T2 target cells under conditions which preserved the viability of the target cells. Therefore, the claimed composition appears to be the same as the antibody of the prior art absent a showing of differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show an unobvious distinction between the composition of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

17. Claims 4-8, 44, 49, 50 and 57 are rejected under 35 U.S.C. 102(b) as being anticipated by Reinelt *et al* (J. Biol. Chem. 276(27): 24525-24530, IDS reference).

Reinelt *et al* teach a panel of β-amino substituted peptides based upon the native RRFFVYYV HLA-B27 binding peptide (an endogenous peptide), with single β-amino acid replacement at each position in the peptide, including at the position 2 and 8 anchor residue positions. Reinelt *et al* teach that β-amino acid substitution at position 2 significantly improves resistance to proteolysis, rapid clearance of peptide from blood being one of the major limitations for the pharmaceutical application of peptides. Reinelt *et al* teach utilization of the β-amino acid substituent peptides for the design of altered MHC ligands for therapeutic application (see entire reference, especially abstract and Table 1).

A with regard to the limitation "pharmaceutically acceptable diluent", although the art reference does not teach the diluent that the peptides are comprised in, it does teach that the peptides are in a solubilizing medium, and it also teaches that in the CTL assay, the peptide was added to the T2 target cells under conditions which preserved the viability of the target cells. Therefore, the claimed composition appears to be the same as the antibody of the prior art absent a showing of differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant invention to those of the prior art, the burden is on Applicant to show an unobvious distinction between the composition of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

18. Claims 4-8, 44, 49-51 and 57 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 02/092120 A1 (IDS reference).

WO 02/092120 A1 exemplifies Melan-A/MART-1 HLA-A2-binding peptides and analogs thereof, including β-Ala P1 substituent peptides and also teaches that the native Melan-A26-35 A27L peptide may be modified at amino acid position 1 or 2 or 8, 9 or 10, which positions 2 and the carboxy terminus are the primary anchor residues for HLA-A2 binding peptides (see entire reference, especially abstract, Tables 1, 1B, IIIA & B, Example 4, claims).

A with regard to the limitation "pharmaceutically acceptable diluent", although the art reference does not teach the diluent that the peptides are comprised in, it does teach that the peptides are in a solubilizing medium, and it also teaches that in the CTL assay, the peptide was added to the T2 target cells under conditions which preserved the viability of the target cells. Therefore, the claimed composition appears to be the same as the antibody of the prior art absent a showing of differences. Since the Patent Office does not have the facilities for examining and comparing the composition of the instant

invention to those of the prior art, the burden is on Applicant to show an unobvious distinction between the composition of the instant invention and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

19. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

20. Claims 4-8, 11, 12, 44, 49-52 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Guichard *et al* (J. Med. Chem. 2000, 43: 3803-3808) in view of Steer *et al* (Curr. Med. Chem. 4/15/2002, 9(8): 811-822) and Micheletti *et al* (Immunol. 1999, 96: 411-415).

Guichard *et al* teach a HLA-A2-binding peptide from tumor antigen Melan-A/MART-1 with a beta amino acid residue substituent at anchor position 2 of the peptide. Guichard *et al* also teach β-amino acid substituents at other positions of the peptide, and compositions comprising each of the peptides. Guichard *et al* further teach that the MART-1 peptide has weak immunogenicity, hence the amino acid substitutions were made in order to study the issue of overcoming said weak immunogenicity. Guichard *et al* that "despite encouraging results, early vaccination trials with peptides derived from gp100, MART-1, tyrosinase, MAGE-1 and MAGE-3 have experienced difficulty in inducing CTL immunity. Guichard *et al* teach that BAGE and GAGE are also tumor antigens. Guichard *et al* teach that they found that in the case of the MART-1 peptide, each central P3-P7 residue with the exception of P5 could be replaced by the corresponding β-amino acid residue without affecting the ability to bind to HLA-A2 molecules. Guichard *et al* also teach that insertion of β-amino acid residues might contribute to increased resistance to enzymatic degradation and therefore might lead to improved *in vivo* activity, particularly relevant in view of the very short half-life of the native MART-1 peptide (see entire reference, especially Table 1).

Guichard *et al* do not teach that the peptide is from MAGE or BAGE nor do they explicitly teach that the peptide is present with a pharmaceutically acceptable carrier or diluent.

Both Steer *et al* and Micheletti *et al* teach β–substituted peptides in a pharmaceutically acceptable carrier or diluent such as PBS as enunciated supra in this Office Action at items #15 and #16.

It would have been prima facie obvious to have made β–substituted peptide analogs for the other weakly immunogenic tumor antigen epitope peptides such as from MAGE-1 or MAGE-3 or BAGE that are taught by Guichard *et al* to be weakly immunogenic as is the MART-1 peptide for which the panel of β–substituted peptides was made, and to have placed the analog peptides (including the MART-1 analog peptides) in a suitable diluent such as PBS.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to test the *in vivo* activity of the peptides, particularly in light of the teaching of Guichard *et al* that β-amino acid substituent peptides may have increased resistance to proteolysis *in vivo*.

21. Claims 4-8, 11, 12, 44, 49-54, 57, 61 and 62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reinelt *et al* (J. Biol. Chem. 276(27): 24525-24530, IDS reference) in view of Chen *et al* (Journal of Immunology 2000, 165: 948-955).

Reinelt *et al* teach a panel of β-amino substituted peptides based upon the native RRFFVYYV HLA-B27 binding peptide (an endogenous peptide), with single β-amino acid replacement at each position in the peptide, including at the position 2 and 8 anchor residue positions. Reinelt *et al* teach that β-amino acid substitution at position 2 significantly improves resistance to proteolysis, rapid clearance of peptide from blood being one of the major limitations for the pharmaceutical application of peptides. Reinelt *et al* teach utilization of the β-amino acid substituent peptides for the design of altered MHC ligands for therapeutic application. Reinelt *et al* teach alteration of positions 3 to the C-terminal residue were insensitive to the substitution in terms of maintenance of binding affinity and thermodynamic stability relative to the native peptide (see entire reference, especially abstract and Table 1).

Reinelt *et al* do not teach making β-amino acid substituent peptides from the NY-ESO-1 peptide SLLMWITQC.

Chen *et al* teach that the cysteine at the c-terminus of the NY-ESO-1 peptide SLLMWITQC is deleterious in terms of antigenicity, due to cysteinylation and dimerization of cysteine residues, in binding to MHC class I HLA-A2. Chen *et al* further teach making V, I, or L substitution for C at position 9, resulting in increased immunogenicity. Chen *et al* teach that identification of highly antigenic NY-ESO-1 peptide analogues may be beneficial for development of vaccines (i.e., composition of peptide comprising a pharmaceutically acceptable carrier) capable of expanding NY-ESO-1 specific T CTL in cancer patients (see entire reference, especially abstract, paragraph spanning pages 948-949, Table 1 and last paragraph).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have made a panel of b-substituted versions of the SLLMWITQC peptide and to have placed it in a composition comprising a pharmaceutically acceptable carrier such as PBS.

One of ordinary skill in the art at the time the invention was made would have been motivated to do this in order to further explore making more immunogenic variants of the native peptide as taught by both Chen *et al* and by Reinelt *et al*, and to make a peptide that is more resistant to proteolysis, particularly in light of the teaching of Reinelt *et al* that β-amino acid substitution may significantly improve resistance to proteolysis, blood clearance being one of the major limitations for the pharmaceutical application of peptides.

22. The following is a quotation of the second paragraph of 35 U.S.C. 112:
> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

23. Claims 49-54, 57 and 61-63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Claims 49-51 and 61 recite "MHC epitope" and base claim 49 recites "with the proviso that said peptide comprises at least 1 β-amino acid substitution at an MHC anchor position in said epitope." If the peptide comprises an MHC epitope of an antigen, it can not comprise a substitution of an anchor residue. The claimed peptide appears to be an analogue peptide of an MHC epitope.

24. No claim is allowed.

25. The peptide recited in instant claim 63 is free of the prior art of record.

26. Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Marianne DiBrino whose telephone number is 571-272-0842. The Examiner can normally be reached on Monday, Tuesday, Thursday and Friday.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Ram Shukla, can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair

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